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FILE 'REGISTRY' ENTERED AT 08:20:09 ON 04 FEB 1999

STRUCTURE FILE UPDATES: 29 JAN 99 HIGHEST RN 218764-34-2
DICTIONARY FILE UPDATES: 3 FEB 99 HIGHEST RN 218897-90-6

TSCA INFORMATION NOW CURRENT THROUGH JUNE 31, 1998

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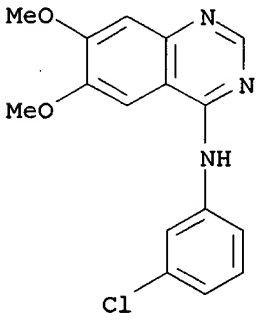
L44 ANSWER 1 OF 1 REGISTRY COPYRIGHT 1999 ACS
RN **153436-53-4** REGISTRY
CN 4-Quinazolinamine, N-(3-chlorophenyl)-6,7-dimethoxy- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN AG 1478
CN Tyrphostin AG 1478
FS 3D CONCORD
DR **175178-82-2**
MF C16 H14 Cl N3 O2
CI COM
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CHEMCATS, TOXLIT, USPATFULL

514/259 544/253



14 REFERENCES IN FILE CA (1967 TO DATE)
14 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:288260

REFERENCE 2: 129:272691

REFERENCE 3: 129:156926

REFERENCE 4: 129:156456

REFERENCE 5: 129:119500

Cisplatin: 424/649
423/351
vincristine: 514/183
540/478
paclitaxel: 514/449
549/510

```
REFERENCE   6:  129:62930

REFERENCE   7:  128:261949

REFERENCE   8:  128:136497

REFERENCE   9:  127:303614

REFERENCE  10:  127:272367

=> d his


     (FILE 'HOME' ENTERED AT 07:49:38 ON 04 FEB 1999)
               SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 07:50:06 ON 04 FEB 1999
               E GAZIT A/AU
L1           102 S E3,E6
               E LEVITZKI A/AU
L2           263 S E3-E5
               E CAVENEE W/AU
L3           107 S E3-E7
               E NAGANE M/AU
L4             7 S E5
               E HUANG H/AU
L5           277 S E3,E18-E20
L6            11 S APOPTO? AND L1-L5
L7            44 S (EGF OR EGFR) AND L1-L5
L8            46 S EPIDERM? (L) GROWTH? AND L1-L5
L9             5 S L6 AND L7,L8
L10           40 S AG1478 OR AG 1478
L11           12 S TYRPHOSTIN(L)1478
               S 153436-53-4/REG#

     FILE 'REGISTRY' ENTERED AT 08:04:53 ON 04 FEB 1999
L12            1 S 153436-53-4/RN

     FILE 'HCAPLUS' ENTERED AT 08:04:54 ON 04 FEB 1999
L13           16 S L12
L14            9 S L1-L5 AND L10,L11,L13
L15            1 S L14 AND L6
L16            9 S L14 AND (EGF OR EGFR OR EPIDERM? (L) GROWTH?)
L17           13 S L9,L14,L15,L16

     FILE 'REGISTRY' ENTERED AT 08:05:58 ON 04 FEB 1999
L18            1 S 62229-50-9
               E .DELTA.-EPIDERMAL/CN
               E .DELTA.-EGF/CN
L19            3 S 15663-27-1 OR 33069-62-4 OR 57-22-7

     FILE 'HCAPLUS' ENTERED AT 08:07:24 ON 04 FEB 1999
L20            4 S L1-L5 AND (L19 OR CISPLATIN? OR PACLITAXEL OR TAXOL OR VINCRI
L21           19 S L1-L5 AND L18

     FILE 'REGISTRY' ENTERED AT 08:09:24 ON 04 FEB 1999
L22            1 S 80449-02-1

     FILE 'HCAPLUS' ENTERED AT 08:09:34 ON 04 FEB 1999
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L23          40 S L22 AND L1-L5
L24           6 S L23 AND L20,L21
L25          15 S L23 AND L6-L11
L26          33 S L6,L9,L17,L20,L24,L25
L27          11 S L21 NOT L26
L28          44 S L27,L26
L29           6 S L28 AND (3 OR 7 OR 9)/SC
L30           2 S L29 AND 2/SX
L31           1 S L30 NOT MODEL/TI
L32           5 S L29 NOT L31
L33          39 S L28 NOT L32
L34          47 S L10,L11,L13
L35           6 S L34 AND APOPTOS?
L36           2 S L34 AND CELL(L)(DEATH OR SURIV?)
L37           2 S L34 AND GLIOM?
L38           2 S L34 AND BREAST
L39           2 S L34 AND MAMMAR?
L40           3 S L34 AND LUNG
L41           3 S L34 AND OVAR?
L42          14 S L35-L41
L43          47 S L34,L42
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 08:16:31 ON 04 FEB 1999
L44           1 S E1-E2

     FILE 'REGISTRY' ENTERED AT 08:17:08 ON 04 FEB 1999

     FILE 'HCAPLUS' ENTERED AT 08:17:22 ON 04 FEB 1999
L45           9 S L43 AND L1-L5
L46          38 S L43 NOT L45

     FILE 'REGISTRY' ENTERED AT 08:20:09 ON 04 FEB 1999

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 08:20:16 ON 04 FEB 1999
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FILE COVERS 1967 - 4 Feb 1999  VOL 130 ISS 6
FILE LAST UPDATED: 4 Feb 1999  (19990204/ED)

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 substance identification.

 This file supports REG1stRY for direct browsing and searching of
 all substance data from the REGISTRY file.  Enter HELP FIRST for
 more information.

=> d 145 bib abs hitrn tot
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L45 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:534888 HCAPLUS
DN 129:156926
TI Methods and compositions using receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders, and inhibitor preparation
IN Chen, Hui; **Gazit, Aviv**; Hirth, Klaus Peter; Mann, Elaina; Shawver, Laura K.; Tsai, Jianming; Tang, Peng Cho
PA Sugen, Inc., USA; Yissum Research & Development Company of the Hebrew University of Jerusalem
SO U.S., 41 pp. Cont.-in-part of U.S. Ser. No. 207,933, abandoned. CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5789427	A	19980804	US 95-399967	19950307
	US 5773476	A	19980630	US 95-486775	19950607
PRAI	US 94-207933		19940307		
	US 95-399967		19950307		

OS MARPAT 129:156926
AB The invention concerns compds. and their use to inhibit the activity of a receptor tyrosine kinase. The invention is preferably used to treat cell proliferative disorders, e.g. cancers characterized by over-activity or inappropriate activity HER2 or EGFR.
IT **153436-53-4P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(receptor tyrosine kinase inhibitors, and prepn. thereof, for inhibiting cell proliferative disorders)

L45 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:400243 HCAPLUS
DN 129:156456
TI Inhibition of Cdk2 activation by selected tyrphostins causes cell cycle arrest at late G1 and S phase
AU Kleinberger-Doron, Nurit; Shelah, Noa; Capone, Ricardo; **Gazit, Aviv; Levitzki, Alexander**
CS Department of Biological Chemistry, Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem, 91904, Israel
SO Exp. Cell Res. (1998), 241(2), 340-351 CODEN: ECREAL; ISSN: 0014-4827
PB Academic Press
DT Journal
LA English
AB The authors have previously reported that certain tryphostins which block EGF-R phosphorylation in cell-free systems fail to do so in intact cells. Nevertheless, the authors found that this family of tyrphostins inhibits both EGF- and calf serum-induced cell growth and DNA synthesis [Osherov, N.A., Gazit, C., Gilon, and Levitzki, A. (1993). Selective inhibition of the EGF and HER2/Neu receptors by Tyrphostins. J. Biol. Chem. 268, 11134-11142.]; now the authors show that these tryphostins exert their inhibitory activity even when added at a time when the cells have already passed their restriction point and receptor activation is no longer necessary. AG555 and AG556 arrest 85% of the cells at late G1, whereas AG490 and AG494 cause cells to arrest at late G1 and during S phase. No arrest occurs during G2 or M phase. Further anal. revealed that these

tyrphostins act by inhibiting the activation of the enzyme Cdk2 without affecting its levels or its intrinsic kinase activity. Furthermore, they do not alter the assocn. of Cdk2 to cyclin E or cyclin A or to the inhibitory proteins p21 and p27. These compds. also have no effect on the activating phosphorylation of Cdk2 by Cdk2 activating kinase (CAK) and no effect on the catalytic domain of cdc25 phosphatase. These compds. lead to the accumulation of phosphorylated Cdk2 on tyrosine 15 which is most probably the cause for its inhibition leading to cell cycle arrest at G1/S. A structure-activity relation study defines a very precise pharmacophore, suggesting a unique mol. target not yet identified and which is most probably involved in the regulation of the tyrosine-phosphorylated state of Cdk2. These compds. represent a new class of cell proliferation blockers whose target is Cdk2 activation. (c) 1998 Academic Press.

IT **153436-53-4, AG1478**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(inhibition of Cdk2 activation by selected tyrphostins causes cell cycle arrest at late G1 and S phase in relation to tyrosine phosphorylation and structure)

L45 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:319418 HCAPLUS
DN 129:62930
TI Inhibition of platelet-derived growth factor and epidermal growth factor receptor signaling events after treatment of cells with specific synthetic inhibitors of tyrosine kinase phosphorylation
AU Lipson, Kenneth E.; Pang, Long; Huber, L. Julie; Chen, Hui; Tsai, Jian-Ming; Hirth, Peter; **Gazit, Aviv; Levitzki, Alexander**; Mcmahon, Gerald
CS SUGEN, Inc., Redwood City, CA, USA
SO J. Pharmacol. Exp. Ther. (1998), 285(2), 844-852
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
AB The receptor kinase activity assocd. with the epidermal growth factor (EGF) receptor and platelet-derived growth factor (PDGF) receptor plays an important role in ligand-induced signaling events. The effect of specific, synthetic chem. inhibitors of PDGF- and EGF-mediated receptor tyrosine autophosphorylation on receptor signaling were examd. in NIH 3T3 cells overexpressing PDGF of EGF receptors. Specific inhibition of ligand-dependent receptor autophosphorylation, PI3K activation, mitogen-activated protein kinase (MAPK) activation, cyclin E-assocd. kinase activity and cell proliferation was measured after treatment of cells with these inhibitors. A synthetic PDGF receptor kinase inhibitor exhibited specific inhibitory properties when tested for PDGF-induced receptor autophosphorylation, MAPK activity, PI3K activation, entry into S phase and cyclin E-assocd. kinase activity. A synthetic EGF receptor kinase inhibitor showed selective inhibitory properties when tested for EGF-induced receptor autophosphorylation, MAPK activation, PI3K activation, entry into S phase and cyclin E-assocd. kinase activity. In both cases, these compds. were found to be effective as inducers of growth arrest and accumulation of cells in the G1 phase of the cell cycle after ligand treatment. However, at high concns., the EGF receptor kinase inhibitor was obsd. to exhibit some non-specific effects as demonstrated by attenuation of PDGF-induced receptor autophosphorylation and cell cycle progression. This demonstrates that it is crit. to use the lowest concn. of such an inhibitor that will alter the response under investigation, to

have confidence that the conclusions derived from the use of such inhibitor are valid. We conclude that these exptl. parameters signify useful end points to measure the relative selectivity of tyrosine kinase inhibitors that affect receptor-mediated signal transduction.

IT **153436-53-4, AG1478**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inhibition of platelet-derived growth factor and epidermal growth factor receptor signaling events after treatment of cells with specific synthetic inhibitors of tyrosine kinase phosphorylation)

L45 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:593456 HCAPLUS
DN 127:272367
TI Inhibitors of epidermal growth factor receptor kinase and of cyclin-dependent kinase 2 activation induce growth arrest, differentiation, and **apoptosis** of human papilloma virus 16-immortalized human keratinocytes
AU Ben-Bassat, Hannah; Rosenbaum-Mitrani, Stella; Hartzstark, Zippora; Shlomai, Zippora; Kleinberger-Doron, Nurit; **Gazit, Aviv**; Plowman, Gregory; Levitzki, Rubina; Tsvieli, Rimona; **Levitzki, Alexander**
CS Laboratory of Experimental Surgery, Hadassah University Hospital, Jerusalem, IL-Q1120, Israel
SO Cancer Res. (1997), 57(17), 3741-3750
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB Human papilloma virus 16 (HPV 16) is assocd. with cervical cancer and is therefore considered a major health risk for women. Immortalization of keratinocytes induced by HPV infection is largely due to the binding of p53 and Rb by the viral oncoproteins E6 and E7, resp., and is driven to a large extent by a transforming growth factor .alpha./amphiregulin epidermal growth factor receptor autocrine loop. In this study, we show that the growth of HPV 16-immortalized human keratinocytes can be blocked by a selective epidermal growth factor receptor kinase inhibitor, **AG 1478**, and by AG 555, a blocker of cyclin-dependent kinase 2 (Cdk2) activation. **AG 1478** induces a massive increase in the Cdk2 protein inhibitors p27 and p21, whereas AG 555 appears to have a different mechanism of action, inhibiting the activation of Cdk2. Growth arrest induced by **AG 1478** and AG 555 is accompanied by up to 20% of cells undergoing **apoptosis**. Following **AG 1478** treatment but not AG 555 treatment, up to 50% of cells undergo terminal keratinocyte differentiation as detd. by filaggrin expression and by the decline in the expression of cytokeratin 14. The growth-arresting properties of **AG 1478** and AG 555 identifies them as possible lead antipapilloma agents.
IT **153436-53-4, AG 1478**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mechanism of antipapilloma activity of **AG 1478** and AG 555)

L45 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:434885 HCAPLUS
DN 127:187332
TI Tyrphostin AG 494 blocks Cdk2 activation
AU Osherov, Nir; **Levitzki, Alexander**

CS Department of Biological Chemistry, Alexander Silverman Institute of Life Sciences, The Hebrew University of Jerusalem, Givat Ram, Jerusalem, 91904, Israel
SO FEBS Lett. (1997), 410(2,3), 187-190
CODEN: FEBLAL; ISSN: 0014-5793
PB Elsevier
DT Journal
LA English
AB We have previously shown that the EGFR kinase selective **tyrphostin** AG 494 fails to inhibit EGFR kinase in intact cells. Yet, AG 494 proved to inhibit EGF- or serum-induced cell proliferation (Osherov et al., J. Biol. Chem. 268 (1993) 11134-11142). In this preliminary communication we show that AG 494 as well as its close analogs AG 490 and AG 555 block Cdk2 activation. In contrast, **AG 1478**, a more selective EGFR kinase blocker which is also active as EGFR kinase blocker in intact cells, fails to do so. AG 494 exerts its full inhibitory activity on Cdk2 activation even when added 20 h subsequent to EGF addn. when Cdk2 activation is maximal. The inhibitory activity on Cdk2 activation parallels its DNA synthesis inhibitory activity, strongly suggesting that its target is one of the mol. mechanisms involved in Cdk2 activation. AG 494 and its analogs may become useful lead compds. for the development of drugs aimed at the cell cycle machinery.

L45 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:572296 HCAPLUS
DN 125:264991
TI Tyrphostins IV-highly potent inhibitors of EGF receptor kinase. Structure-activity relationship study of 4-anilidoquinazolines
AU **Gazit, Aviv**; Chen, Jeffrey; App, Harald; McMahon, Gerald; Hirth, Peter; Chen, Irit; **Levitzki, Alexander**
CS Alexander Silverman Inst. Life Sci., Hebrew Univ. Jerusalem, Jerusalem, 91904, Israel
SO Bioorg. Med. Chem. (1996), 4(8), 1203-1207
CODEN: BMECEP; ISSN: 0968-0896
DT Journal
LA English
AB Potent 4-anilido-substituted quinazolines which potently inhibit epidermal growth factor receptor (EGFR) kinase were prepd. Structure-activity relation studies reveal high sensitivity to substitution at the aniline ring.
IT **153436-53-4P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and structure-activity relationship study of anilidoquinazolines as EGF receptor kinase inhibitors)

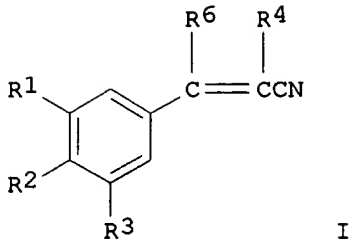
L45 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:530427 HCAPLUS
DN 125:185163
TI **Tyrphostin AG 1478** preferentially inhibits human **glioma** expressing truncated rather than wild-type epidermal growth factor receptors
AU Han, Yuchun; Caday, Cornelio Gacusana; Nanda, Anil; **Cavenee, Webster K.**; **Huang, H-J.**
CS Biomedical Res. Inst., Louisiana State Univ. Med. Cent., Shreveport, LA, 71130, USA
SO Cancer Res. (1996), 56(17), 3859-3861
CODEN: CNREA8; ISSN: 0008-5472

DT Journal
LA English
AB The effects of a new epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, **tyrphostin AG 1478**, were tested on three related human **glioma** cell lines: U87MG, which expressed endogenous wild-type (wt.) EGFR, and two retrovirally infected U87MG cell populations which overexpressed either wt. (U87MG.wtEGFR) or truncated EGFR (U87MG..DELTA.EGFR). Although **AG 1478** inhibited cell growth, DNA synthesis, EGFR tyrosine kinase activity, and receptor autophosphorylation of each cell line tyrosine kinase activity, and receptor autophosphorylation of each cell line in a dose-dependent manner, it was significantly more potent in U87MG..DELTA.EGFR cells than in the other two cell lines. The increased inhibitory response of U87MG..DELTA.EGFR cells was due to a greater sensitivity of the constitutively autophosphorylated Mr 140,000 and 155,000 .DELTA.EGFR species to **AG 1478**. These results suggest that **AG 1478** is a relatively specific inhibitor of the .DELTA.EGFR, and this finding may have important therapeutic implications since the .DELTA.EGFR occurs frequently in glioblastomas and in **breast**, **lung**, and **ovarian** cancers.
IT **153436-53-4, Tyrphostin AG 1478**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**tyrphostin AG 1478** preferentially inhibits human **glioma** expressing truncated rather than wild-type epidermal growth factor receptors)

L45 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1995:926425 HCAPLUS
DN 123:329984
TI Receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders
IN Chen, Hui; **Gazit, Aviv**; Hirth, Klaus Peter; **Levitzki, Alex**; Mann, Elaina; Shawver, Laura K.; Tsai, Jianming; Tang, Peng Cho
PA Sugen, Inc., USA; Yissum Research Development Co.
SO PCT Int. Appl., 121 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9524190	A2	19950914	WO 95-US2826	19950306
	WO 9524190	A3	19951109		
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9520968	A1	19950925	AU 95-20968	19950306
PRAI	US 94-207933		19940307		
	WO 95-US2826		19950306		

OS MARPAT 123:329984
GI



I

AB Receptor tyrosine kinase inhibitors I [R1-R3, R6 = alkyl, alkenyl, alkynyl, alkoxy, OH, amino, SH, alkylthio, halo, H, NO2, etc.; R4 = C(S)NHR5, C(O)NHR5, SO2YR5; Y = single bond, C(CN):CH:CH, azaalkyl; R5 = (substituted) aralkyl, CN] and II [R7-R10 = R1-R3 above; R12 = C(O)Me, C(S)Me, C(O)CF3, C(S)CF3; R13 = aryl, alkylaryl] are prepd. for use in treating cell proliferative disorders such as cancers characterized by overactivity or inappropriate activity of HER2 receptors or EGF receptors. Thus, I [R1, R2 = OH, R3 = I, R4 = C(O)NH(CH2)3Ph, R6 = H] (III) was prepd. in 2 steps by condensation of 5-iodovanillin with N-(3-phenylpropyl)cyanoacetamide. III inhibited EGF receptor kinase activity in EGC7 cells, HER2 kinase activity in BT-474 cells, and platelet-derived growth factor receptor kinase .beta. activity with an IC50 of 4, 18, and 35 .mu.M, resp., and inhibited growth of SKBR3 and SKOV3 cells in vitro at IC50 9 and 4.5 .mu.M, resp.

IT **153436-53-4P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(receptor tyrosine kinase inhibitors for inhibiting cell proliferative disorders)

L45 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 1999 ACS
AN 1994:647079 HCAPLUS
DN 121:247079
TI Epidermal growth factor-dependent activation of the Src-family kinases
AU Osherov, Nir; **Levitzki, Alexander**
CS Alexander Silberman Inst. Life Sci., Hebrew Univ. Jerusalem, Jerusalem, 91904, Israel
SO Eur. J. Biochem. (1994), 225(3), 1047-53
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English
AB The precise role of src-type kinases as signal transducers has been under intensive investigation but only in a few instances has their role been revealed in any detail. Thus, src, fyn and yes are activated upon stimulation by platelet-derived growth factor or colony-stimulating factor in cells expressing high levels of these receptors. Activation of src-family kinases by other receptor tyrosine kinases such as the epidermal-growth-factor (EGF) receptor has not been directly demonstrated. In this report, we demonstrate EGF-dependent activation of src-family tyrosine kinases in NIH3T3 cells overexpressing the human EGF receptor. Activation is rapid (<1 min) and persistent (up to 16 h). Furthermore, we show a correlation between the level of EGF receptor expressed and the degree of src-family kinase activation. We show that src-family kinase activity is also activated by addn. of EGF to PC12 cells, which endogenously express relatively high levels of EGF receptor. Most strikingly, we show that A431 cells, which endogenously express very high

levels of EGF receptor, show 10-fold elevated src-family kinase activity as compared to DHER14 cells, and that this activity is constitutive. This activity is completely blocked by **AG1478**, a specific inhibitor of the EGF-receptor tyrosine kinase activity, pointing to a direct link between overexpression of the EGF receptor and enhanced src-family kinase activity. Our findings suggest that EGF-dependent src-family kinase activity is detectable only when the levels of EGF receptor reach a specific level. Addnl., high levels of EGF receptor, as in A431 cells, may contribute to the elevated activation of src-family kinases. Sustained src-family kinase activation, similar to that seen in v-src-transformed cells, may play a role in tumorigenesis and tumor maintenance.

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L49 ANSWER 1 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1999:57935 HCAPLUS
TI Gastrin induces heparin-binding epidermal growth factor-like growth factor in rat gastric epithelial cells transfected with gastrin receptor
AU Miyazaki, Yoshiji; Shinomura, Yasuhisa; Tsutsui, Shusaku; Zushi, Shinichiro; Higashimoto, Yoshifumi; Kanayama, Shuji; Higashiyama, Shigeki; Taniguchi, Naoyuki; Matsuzawa, Yuji
CS Department of Internal Medicine and Molecular Science, Graduate School of Medicine, Osaka University, Osaka, Japan
SO Gastroenterology (1999), 116(1), 78-89
CODEN: GASTAB; ISSN: 0016-5085
PB W. B. Saunders Co.
DT Journal
LA English
AB Parietal cells express heparin-binding epidermal growth factor (EGF)-like growth factor (HB-EGF). However, it is unknown whether HB-EGF mediates the trophic action of gastrin. The purpose of this study was to det. whether gastrin modulates the expression of HB-EGF, which mediates the proliferative effects of gastrin on gastric epithelial cells. RGM1 cells, a rat gastric epithelial cell line, were transfected with a human gastrin receptor complementary DNA. Gastrin induction of mRNAs (mRNAs) for EGF-related polypeptides was assayed by Northern blotting. Processing of cell surface-assocd. proHB-EGF and secretion of HB-EGF were detd. by flow cytometry and Western blotting, resp. Tyrosine phosphorylation of the EGF receptor was assayed by immunopptn. and Western blotting with an antiphosphotyrosine antibody. Cell growth was evaluated by [3H]thymidine incorporation. Gastrin induced expression of HB-EGF mRNA, processing of proHB-EGF, release of HB-EGF into the medium, and tyrosine phosphorylation of the EGF receptor. The growth-stimulatory effects of gastrin were partly inhibited by anti-rat HB-EGF serum and completely blocked by **AG1478**, an EGF receptor-specific tyrphostin. The findings suggest that HB-EGF at least partially mediates the proliferative effects of gastrin on gastric epithelial cells.

L49 ANSWER 2 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1999:20121 HCAPLUS
TI Arachidonate-induced tyrosine phosphorylation of epidermal growth factor receptor and Shc-Grb2-Sos association
AU Dulin, Nickolai O.; Sorokin, Andrey; Douglas, Janice G.
CS Division of Hypertension, Department of Medicine, Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, OH, 44106-4982, USA
SO Hypertension (1998), 32(6), 1089-1093

CODEN: HPRTDN; ISSN: 0194-911X
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Protein tyrosine phosphorylation induced by arachidonic acid (AA), an important lipid second messenger, was investigated in rabbit renal proximal tubule epithelial cells. AA stimulated tyrosine phosphorylation of a no. of proteins with estd. mol. wts. of 42, 44, 52, 56, 85, and 170/180 kDa. The phosphoproteins pp44 and pp42 were identified as 2 isoforms of mitogen-activated protein kinase (MAPK). Phosphorylation of MAPK in response to AA was transient, dose-dependent, and accompanied by an increase in its activity. The mechanism of AA-induced MAPK activation in RTE cells was protein kinase C-independent and involved tyrosine phosphorylation of adaptor protein Shc and its assocn. with Grb2-Sos complex. Moreover, stimulation of RTE cells with AA resulted in significant phosphorylation of epidermal growth factor (EGF) receptor and its assocn. with Shc. The effect of AA on EGF receptor phosphorylation, its assocn. with Shc, and MAPK activation was similar to the effect of 1 ng/mL EGF. Tyrphostin **AG1478**, a specific inhibitor of EGF receptor tyrosine kinase activity, completely blocked the effects of AA and EGF but not phorbol ester on MAPK phosphorylation. These data suggest that in renal tubular epithelial cells, the mechanism of AA-induced MAPK activation involves tyrosine phosphorylation of EGF receptor and its assocn. with Shc and Grb2-Sos complex. Given the crit. role of AA in signaling linked to G protein-coupled receptors (GPCRs), these observations provide a mechanism for cross talk between GPCRs linked to phospholipases and the tyrosine kinase receptor signaling cascades.

L49 ANSWER 3 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:799051 HCAPLUS
TI Integrins induce activation of EGF receptor: role in MAP kinase induction and adhesion-dependent cell survival
AU Moro, Laura; Venturino, Mascia; Bozzo, Chiarella; Silengo, Lorenzo; Altruda, Fiorella; Beguinot, Laura; Tarone, Guido; Defilippi, Paola
CS Dipartimento di Scienze Mediche, Novara, Italy
SO EMBO J. (1998), 17(22), 6622-6632
CODEN: EMJODG; ISSN: 0261-4189
PB Oxford University Press
DT Journal
LA English
AB Adhesion of human primary skin fibroblasts and ECV304 endothelial cells to immobilized matrix proteins, .beta.1 or .alpha.v integrin antibodies stimulates tyrosine phosphorylation of the epidermal growth factor (EGF) receptor. This tyrosine phosphorylation is transiently induced, reaching maximal levels 30 min after adhesion, and it occurs in the absence of receptor ligands. Similar results were obsd. with EGF receptor-transfected NIH-3T3 cells. Use of a kinase-neg. EGF receptor mutant demonstrates that the integrin-stimulated tyrosine phosphorylation is due to activation of the receptor's intrinsic kinase activity. Integrin-mediated EGF receptor activation leads to Erk-1/MAP kinase induction, as shown by treatment with the specific inhibitor tyrphostin **AG1478** and by expression of a dominant-neg. EGF receptor mutant. EGF receptor and Erk-1/MAP kinase activation by integrins does not lead per se to cell proliferation, but is important for entry into S phase in response to EGF or serum. EGF receptor activation is also required for extracellular matrix-mediated cell survival. Adhesion-dependent MAP kinase activation and survival are regulated through EGF receptor activation in cells expressing this mol. above a threshold level (5 .times. 103 receptors per cell). These results demonstrate that

integrin-dependent EGF receptor activation is a novel signaling mechanism involved in cell survival and proliferation in response to extracellular matrix.

L49 ANSWER 4 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:700247 HCAPLUS
DN 130:33349
TI Carbachol stimulates transactivation of epidermal growth factor receptor and mitogen-activated protein kinase in T84 cells. Implications for carbachol-stimulated chloride secretion
AU Keely, Stephen J.; Uribe, Jorge M.; Barrett, Kim E.
CS Department of Medicine, School of Medicine, University of California, San Diego, San Diego, CA, 92103, USA
SO J. Biol. Chem. (1998), 273(42), 27111-27117
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB The authors have examd. the role of tyrosine phosphorylation in regulation of calcium-dependent chloride secretion across T84 colonic epithelial cells. The calcium-mediated agonist carbachol (CCh, 100 .mu.M) stimulated a time-dependent increase in tyrosine phosphorylation of a range of proteins (with mol. masses ranging up to 180 kDa) in T84 cells. The tyrosine kinase inhibitor, genistein (5 .mu.M), significantly potentiated chloride secretory responses to CCh, indicating a role for CCh-stimulated tyrosine phosphorylation in neg. regulation of CCh-stimulated secretory responses. Further studies revealed that CCh stimulated an increase in both phosphorylation and activity of the extracellular signal-regulated kinase (ERK) isoforms of mitogen-activated protein kinase. Chloride secretory responses to CCh were also potentiated by the mitogen-activated protein kinase inhibitor, PD98059 (20 .mu.M). Phosphorylation of ERK in response to CCh was mimicked by the protein kinase C (PKC) activator, phorbol myristate acetate (100 nM), but was not altered by the PKC inhibitor GF 109203X (1 .mu.M). ERK phosphorylation was also induced by epidermal growth factor (EGF) (100 ng/mL). Immunopptn./Western blot studies revealed that CCh stimulated tyrosine phosphorylation of the EGF receptor (EGFr) and increased co-immunopptn. of the adapter proteins, Shc and Grb2, with the EGFr. An inhibitor of EGFr phosphorylation, tyrphostin **AG1478** (1 .mu.M), reversed CCh-stimulated phosphorylation of both EGFr and ERK. Tyrphostin **AG1478** also potentiated chloride secretory responses to CCh. The authors conclude that CCh activates ERK in T84 cells via a mechanism involving transactivation of the EGFr, and that this pathway constitutes an inhibitory signaling pathway by which chloride secretory responses to CCh may be neg. regulated.

L49 ANSWER 5 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:685050 HCAPLUS
DN 129:272691
TI Detection of molecular and protein interactions by reporter subunit complementation
IN Blau, Helen M.; Rossi, Fabio; Mohler, William
PA The Board of Trustees of the Leland Stanford Junior University, USA
SO PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI WO 9844350 A1 19981008 WO 98-US6648 19980402
W: CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRAI US 97-42576 19970402
US 97-54638 19970804
AB Methods and compns. for detecting mol. interactions, particularly protein-protein interactions, are provided. The invention allows detection of such interactions in living cells or in vitro. Detection of mol. interactions in living cells is not limited to the nuclear compartment, but can be accomplished in the cytoplasm, cell surface, organelles, or between these entities. In one embodiment, the method utilizes novel compns. comprising fusion proteins between the mols. of interest and two or more inactive, weakly-complementing .beta.-galactosidase mutants. Assocn. between the mols. of interest brings the complementing .beta.-galactosidase mutants into proximity so that complementation occurs and active .beta.-galactosidase is produced. The active .beta.-galactosidase may be detected by methods well-known in the art. Among the uses of the invention are the study of protein-protein interactions, functional genomics, agonist and antagonist screening and drug discovery.
IT **153436-53-4, Tyrphostin AG 1478**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(detection of mol. and protein interactions by reporter subunit complementation)

L49 ANSWER 6 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:683769 HCAPLUS
TI STAT3 mediates the survival signal in oncogenic ras-transfected intestinal epithelial cells
AU Zushi, Shinichiro; Shinomura, Yasuhisa; Kiyohara Tatsuya; Miyazaki, Yoshiji; Kondo, Shinya; Sugimachi, Masamitsu; Higashimoto, Yoshifumi; Kanayama, Shuji; Matsuzava, Yuji
CS Second Department of Internal Medicine, Osaka University Medical School, Suita, 565, Japan
SO Int. J. Cancer (1998), 78(3), 326-330
CODEN: IJCNAW; ISSN: 0020-7136
PB Wiley-Liss, Inc.
DT Journal
LA English
AB The oncogenic ras mutation is a common and crit. step in gastrointestinal carcinogenesis. In a previous study, the authors demonstrated that oncogenic ras activated the EGF-related peptide autocrine loop and that the **apoptosis** resistance obsd. in the oncogenic ras-stimulated cell (IEC-ras cell) was dependent on this activated EGF-related peptide autocrine loop. STATs (signal transducers and activators of transcription), first identified as intracellular signal transducers stimulated by cytokines, are known to also be activated by EGF. However, the role of STATs in the survival signal of IEC-ras cells is not clear. In the present study, the authors demonstrate that STAT3 is constitutively activated in ras-stimulated cells and that STAT3 activation is considerably suppressed by the EGF-specific receptor kinase inhibitor **AG1478**. The authors also show that disruption of the STAT3 pathway by introduction of a dominant-neg. STAT3 mutant abolishes the **apoptosis** resistance against UVC and MMC treatment obsd. in IEC-ras cells without affecting proliferation. Moreover, the expression of Bcl-2 and Bcl-xL, **apoptosis**-suppressive proteins, is reduced in dominant-neg. STAT3-transfected cells. Thus, STAT3 appears to be an

important mediator of the anti-apoptotic signal in IEC-ras cells.

L49 ANSWER 7 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:617822 HCAPLUS
DN 129:314372
TI Mechanical stretch induces hypertrophic responses in cardiac myocytes of angiotensin II type 1a receptor knockout mice
AU Kudoh, Sumiyo; Komuro, Issei; Hiroi, Yukio; Zou, Yunzeng; Harada, Koichiro; Sugaya, Takeshi; Takekoshi, Noboru; Murakami, Kazuo; Kadowaki, Takashi; Yazaki, Yoshio
CS Department of Cardiovascular Medicine, University of Tokyo School of Medicine, Tokyo, 113-8655, Japan
SO J. Biol. Chem. (1998), 273(37), 24037-24043
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Many lines of evidence have suggested that angiotensin II (AngII) plays an important role in the development of cardiac hypertrophy through AngII type 1 receptor (AT1). To det. whether AngII is indispensable for the development of mech. stress-induced cardiac hypertrophy, the authors examd. the activity of mitogen-activated protein kinase (MAPK) family and the expression of the c-fos gene as hypertrophic responses after stretching cultured cardiac myocytes of AT1a knockout (KO) mice. When cardiac myocytes were stretched by 20% for 10 min, extracellular signal-regulated protein kinases (ERKs) were strongly activated in KO cardiomyocytes as well as wild type (WT) myocytes. Both basal and stimulated levels of ERKs were higher in cardiomyocytes of KO mice than in those of WT mice. Activation of another member of the MAPK family, p38MAPK, and expression of the c-fos gene were also induced by stretching cardiac myocytes of both types of mice. An AT1 antagonist attenuated stretch-induced activation of ERKs in WT cardiomyocytes but not in KO cardiomyocytes. Down-regulation of protein kinase C inhibited stretch-induced ERK activation in WT cardiomyocytes, whereas a broad spectrum tyrosine kinase inhibitor (genistein) and selective inhibitors of epidermal growth factor receptor (tyrphostin, **AG1478**, and B42) suppressed stretch-induced activation of ERKs in KO cardiac myocytes. Epidermal growth factor receptor was phosphorylated at tyrosine residues by stretching cardiac myocytes of KO mice. These results suggest that mech. stretch could evoke hypertrophic responses in cardiac myocytes that lack the AT1 signaling pathway possibly through tyrosine kinase activation.

L49 ANSWER 8 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:592709 HCAPLUS
DN 129:298670
TI Related adhesion focal tyrosine kinase and the epidermal growth factor receptor mediate the stimulation of mitogen-activated protein kinase by the G-protein-coupled P2Y2 receptor. Phorbol ester or [Ca2+]i elevation can substitute for receptor activation
AU Soltoff, Stephen P.
CS Division of Signal Transduction, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, 02215, USA
SO J. Biol. Chem. (1998), 273(36), 23110-23117
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB The activation of growth factor receptors and receptors coupled to

heterotrimeric guanine nucleotide-binding proteins (G-proteins) can increase mitogen-activated protein (MAP) kinase activity in many cells. Previously, the authors demonstrated that the activation of G-protein-coupled P2Y2 receptors by extracellular ATP and UTP stimulated MAP (p42 ERK2) kinase by a mechanism that was dependent on the elevation of [Ca2+]i and the activation of related adhesion focal tyrosine kinase (RAFTK) (also called PYK2, CAK.beta., and CADTK) and protein kinase C (PKC). Here, the authors examine further the signaling cascade between the P2Y2 receptor and MAP kinase. MAP kinase was transiently activated by exposure of PC12 cells to UTP. UTP, ionomycin, and phorbol ester (phorbol 12-myristate 13-acetate) increased MAP kinase activity and also promoted the tyrosine phosphorylation of RAFTK, the epidermal growth factor (EGF) receptor, SHC, and p120cbl. Down-regulation of PKC and inhibition of the elevation of [Ca2+]i, conditions that block the activation of MAP kinase, also blocked the increases in the tyrosine phosphorylation of RAFTK and the EGF receptor. **AG1478**, a tyrphostin selective for the EGF receptor, reduced the activation of MAP kinase, the tyrosine phosphorylation of SHC, the assocn. of Grb2 with SHC, and the tyrosine phosphorylation of the EGF receptor and p120cbl but did not block the tyrosine phosphorylation of RAFTK. The similar effects of UTP, ionomycin, and phorbol 12-myristate 13-acetate (PMA) on these signaling proteins demonstrate that the two signaling mols. from phosphatidylinositol 4,5-bisphosphate hydrolysis ([Ca2+]i, from inositol 1,4,5-trisphosphate prodn., and diacylglycerol) can individually initiate the activation of MAP kinase in an EGF receptor-dependent manner. These results demonstrate that the P2Y2 receptor-mediated transactivation of the EGF receptor occurs at a point downstream of RAFTK and indicate that the EGF receptor is required for P2Y2 receptor-mediated MAP kinase activation. Although P2Y2 and EGF receptors may both activate a similar multiprotein signaling cascade immediately upstream of MAP kinase, the P2Y2 receptor appears to uniquely utilize [Ca2+]i, PKC, and, subsequently, RAFTK.

L49 ANSWER 9 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:583555 HCAPLUS
DN 129:288260
TI Opposing effects of cyclosporin A and **tyrphostin AG-1478** indicate a role for Src protein in the cellular control of mineralization
AU Stekelenburg, Jaqueline; Klein, Benjamin Y.; Ben-Bassat, Hannah; Rojansky, Nathan
CS Laboratory of Experimental Surgery, Hadassah Medical Center, Jerusalem, Israel
SO J. Cell. Biochem. (1998), 71(1), 116-126
CODEN: JCEBD5; ISSN: 0730-2312
PB Wiley-Liss, Inc.
DT Journal
LA English
AB Cyclosporin A (CsA) induces osteoporosis but not through direct activation of osteoclasts. CsA also inhibits cell-mediated mineralization in marrow stromal cell culture, whereas the **tyrphostin AG-1478** increases mineralization. These antagonistic effects on mineralization were used to discern mols. that underwent phosphorylation changes in assocn. with their opposing effects on mineralization. In parallel, quant. changes in Src protein were followed. Multiple dexamethasone (DEX)-stimulated stromal cell cultures were grown with and without a mineralization-inhibiting dose (0.1 .mu.M) of CsA and were harvested on different days of DEX stimulation. Immunoblots of gel-fractionated cell exts. showed that the most noticeable changes in tyrosine phosphorylated proteins (TPP) were seen on day 8 of DEX

stimulation. At least 15 TPP bands, mostly smaller than 53 kDa, were more prominent in CsA-treated cultures on day 8. Under CsA, Src protein quantity decreased on day 8, but its cleavage product (52/54 kDa) was sixfold more abundant then on day 7. Day 8 was chosen to test the effect of **AG-1478** on the CsA-induced TPP changes. DMSO (DMSO) alone, the solvent of **AG-1478**, increased mineralization in CsA-treated vs. CsA-untreated cultures and slightly decreased Src and its cleavage product. **AG-1478** at 5 .mu.M, in CsA cultures increased the specific alk. phosphatase activity threefold, with a slight change in mineralization relative to controls grown with DMSO alone. This was accompanied by decreased intensity of several TPP bands smaller than 36 kDa. In contrast, treatment with 50 .mu.M of **AG-1478** increased the intensity of TPP bands at the same mol. size range. This high **AG-1478** dose decreased cell counts selecting mineralizing cells. The results indicate that increased Src protein cleavage product on day 8 by CsA is assocd. with mineralization inhibition, which is opposed by DMSO and 50-.mu.M **AG-1478**, thus antagonizing the effect of CsA on mineralization. Direct or indirect interaction between Src and TPP, antagonistically affected by CsA and **AG-1478**, is likely to underlay cellular control of mineralization. Changes in p19 and p29 intensity showed assocn. with mineralization that was reflected by a significant direct and inverse correlation, resp., with calcium pptn. per cell.

IT **153436-53-4, AG-1478**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(opposing effects of cyclosporin A and **tyrphostin AG -1478** indicate a role for Src protein in cellular control of mineralization)

L49 ANSWER 10 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:560525 HCAPLUS
DN 129:273917
TI Activation of NF-.kappa.B by oncogenic Raf in HEK 293 cells occurs through autocrine recruitment of the stress kinase cascade
AU Troppmair, Jakob; Hartkamp, Jorg; Rapp, Ulf R.
CS Institut fur Medizinische Strahlenkunde und Zellforschung (MSZ), University of Wurzburg, Wurzburg, 97078, Germany
SO Oncogene (1998), 17(6), 685-690
CODEN: ONCNES; ISSN: 0950-9232
PB Stockton Press
DT Journal
LA English
AB Raf-1 kinase has been implicated in the induction of NF-.kappa.B activity by serum growth factors, phorbol ester and PTK oncogenes. Here the authors show that Raf activation of NF-.kappa.B, as measured in reporter gene assays, occurs indirectly and requires the stress kinase cascade. The stress pathway presumably becomes activated through induction of an autocrine loop by activated Raf (Raf-BXB) as suramin, the tyrphostin **AG1478** and a dominant neg. mutant of the EGF-R blocked NF-.kappa.B activation. Raf-BXB synergizes with SAPKs and a dominant neg. mutant of SEK significantly reduces activation of NF-.kappa.B consistent with a role of this signaling pathway in the activation of NF-.kappa.B.

L49 ANSWER 11 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:560358 HCAPLUS
DN 129:256352
TI Tumor promoter arsenite activates extracellular signal-regulated kinase

through a signaling pathway mediated by epidermal growth factor receptor and Shc
AU Chen, Wei; Martindale, Jennifer L.; Holbrook, Nikki J.; Liu, Yusen
CS Gene Expression and Aging Section, Laboratory of Biological Chemistry, National Institute on Aging, Baltimore, MD, 21224, USA
SO Mol. Cell. Biol. (1998), 18(9), 5178-5188
CODEN: MCEBD4; ISSN: 0270-7306
PB American Society for Microbiology
DT Journal
LA English
AB Although arsenite is an established carcinogen, the mechanisms underlying its tumor-promoting properties are poorly understood. Previously, we reported that arsenite treatment leads to the activation of the extracellular signal-regulated kinase (ERK) in rat PC12 cells through a Ras-dependent pathway. To identify potential mediators of the upstream signaling cascade, we examd. the tyrosine phosphorylation profile in cells exposed to arsenite. Arsenite treatment rapidly stimulated tyrosine phosphorylation of several proteins in a Ras-independent manner, with a pattern similar to that seen in response to epidermal growth factor (EGF) treatment. Among these phosphorylated proteins were three isoforms of the proto-oncoprotein Shc as well as the EGF receptor (EGFR). Tyrosine phosphorylation of Shc allowed for enhanced interactions between Shc and Grb2 as identified by coimmunopptn. expts. The arsenite-induced tyrosine phosphorylation of Shc, enhancement of Shc and Grb2 interactions, and activation of ERK were all drastically reduced by treatment of cells with either the general growth factor receptor poison suramin or the EGFR-selective inhibitor tyrphostin **AG1478**. Down-regulation of EGFR expression through pretreatment of cells with EGF also attenuated ERK activation and Shc tyrosine phosphorylation in response to arsenite treatment. These results demonstrate that the EGFR and Shc are crit. mediators in the activation of the Ras/ERK signaling cascade by arsenite and suggest that arsenite acts as a tumor promoter largely by usurping this growth factor signaling pathway.

L49 ANSWER 12 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:414352 HCAPLUS
DN 129:131660
TI Angiotensin II type 1 receptor-induced extracellular signal-regulated protein kinase activation is mediated by Ca2+/calmodulin-dependent transactivation of epidermal growth factor receptor
AU Murasawa, Satoshi; Mori, Yasukiyo; Nozawa, Yoshihisa; Gotoh, Noriko; Shibuya, Masabumi; Masaki, Hiroya; Maruyama, Katsuya; Tsutsumi, Yoshiaki; Moriguchi, Yasutaka; Shibazaki, Yasunobu; Tanaka, Yohko; Iwasaka, Toshiji; Inada, Mitsuo; Matsubara, Hiroaki
CS Department of Medicine II, Kansai Medical University, Osaka, 570, Japan
SO Circ. Res. (1998), 82(12), 1338-1348
CODEN: CIRUAL; ISSN: 0009-7330
PB Williams & Wilkins
DT Journal
LA English
AB The signaling cascade elicited by angiotensin II (Ang II) resembles that characteristic of growth factor stimulation, and recent evidence suggests that G protein-coupled receptors transactivate growth factor receptors to transmit mitogenic effects. In the present study, we report the involvement of epidermal growth factor receptor (EGF-R) in Ang II-induced extracellular signal-regulated kinase (ERK) activation, c-fos gene expression, and DNA synthesis in cardiac fibroblasts. Ang II induced a rapid tyrosine phosphorylation of EGF-R in assocn. with phosphorylation of Shc protein and ERK activation. Specific inhibition of EGF-R function by

either a dominant-neg. EGF-R mutant or selective tyrphostin **AG1478** completely abolished Ang II-induced ERK activation. Induction of c-fos gene expression and DNA synthesis were also abolished by the inhibition of EGF-R function. Calmodulin or tyrosine kinase inhibitors, but not protein kinase C (PKC) inhibitors or downregulation of PKC, completely abolished transactivation of EGF-R by Ang II or the Ca2+ ionophore A 23187. EGF activity in concd. supernatant from Ang II-treated cells was not detected, and satn. of culture media with anti-EGF antibody did not affect the Ang II-induced transactivation of EGF-R. Conditioned media in which cells were incubated with Ang II could not induce phosphorylation of EGF-R on recipient cells. Platelet-derived growth factor-.beta. receptor was not phosphorylated on Ang II stimulation, and Ang II-induced c-jun gene expression was not affected by tyrphostin **AG1478**. Our results demonstrated that in cardiac fibroblasts Ang II-induced ERK activation and its mitogenic signals are dominantly mediated by EGF-R transactivated in a Ca2+/calmodulin-dependent manner and suggested that the effects of Ang II on cardiac fibroblasts should be interpreted in assocn. with the signaling pathways regulating cellular proliferation and/or differentiation by growth factors.

L49 ANSWER 13 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:323483 HCAPLUS
DN 129:119500
TI Inhibitors of the epidermal growth factor receptor protein tyrosine kinase. A quantitative structure-activity relationship analysis
AU Singh, P.; Kumar, R.
CS Department Chemistry, S. K. Government College, Sikar, 332001, India
SO J. Enzyme Inhib. (1998), 13(2), 125-134
CODEN: ENINEG; ISSN: 8755-5093
PB Harwood Academic Publishers
DT Journal
LA English
AB Hansch and Free-Wilson analyses are described on a data set, 4-anilinoquinazolines [the analogs of 4-(3-bromo-anilino)-6,7-dimethoxy quinazoline: PD 153035], as inhibitors of the epidermal growth factor receptor protein tyrosine kinase. These analyses have helped to ascertain the role of different substituents in explaining the obsd. inhibitory activities. From both approaches, it is concluded that the combined electron-donating nature of R1- and R2-substitutions of the quinazoline ring and the electron-withdrawing nature of the X-substitution of the anilino-ring are beneficial for increasing the inhibition activity of a compd. Further, the sym. alkoxy substituents present at the R1- and R2-positions are also engaged in a steric interaction which was detd. quant. through the parabolic relationship between the activity and combined molar refraction parameter, .SIGMA.MR of the substituents.
IT **153436-53-4**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(quant. structure-activity relationship of inhibitors of the epidermal growth factor receptor protein tyrosine kinase)

L49 ANSWER 14 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:312801 HCAPLUS
DN 129:50062
TI Endothelin-1 stimulates DNA synthesis of vascular smooth-muscle cells through transactivation of epidermal growth factor receptor
AU Iwasaki, Hiroaki; Eguchi, Satoru; Marumo, Fumiaki; Hirata, Yukio
CS Second Department of Internal Medicine, Tokyo Medical and Dental University, Tokyo, 113, Japan

SO J. Cardiovasc. Pharmacol. (1998), 31(Suppl. 1, Endothelin V), S182-S184
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott-Raven Publishers
DT Journal
LA English
AB To elucidate the mol. mechanism of the mitogenic effect of endothelin-1 (ET-1) on vascular smooth muscle cells (VSMCs), we studied the effect of **AG1478**, a novel epidermal growth factor receptor (EGFR) kinase inhibitor, on p42/44 mitogen-activated protein (MAP) kinase activation, c-Fos expression, and DNA synthesis stimulated by ET-1. **AG1478** dose-dependently (2.5.times.10-8 M-2.5.times.10-7 M) inhibited ET-1-induced MAP kinase activation. The ET-1-induced c-Fos protein expression was inhibited by **AG1478** (2.5.times.10-7 M). **AG1478** also dose-dependently inhibited ET-1-stimulated [3H]thymidine incorporation. These data suggest that ET-1 induces MAP kinase activation, c-Fos expression, and promotes proliferation of VSMCs via transactivation of EGFR.

L49 ANSWER 15 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:278244 HCAPLUS
DN 129:23683
TI Effect of tyrosine kinase inhibition on surfactant protein A gene expression during human **lung** development
AU Klein, Jonathan M.; DeWild, Louis J.; McCarthy, Troy A.
CS Department of Pediatrics, University of Iowa, Iowa City, IA, 52242-1083, USA
SO Am. J. Physiol. (1998), 274(4, Pt. 1), L542-L551
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
AB Epidermal growth factor (EGF) stimulates surfactant protein (SP) A synthesis in human fetal **lung** explants. Ligand binding to the EGF receptor stimulates an intrinsic receptor tyrosine kinase with subsequent activation of second messengers. We hypothesized that inhibition of EGF-receptor tyrosine kinase activity would block SP-A expression in spontaneously differentiating cultured human fetal **lung** tissue. Mid-trimester fetal **lung** explants were exposed for 4 days to genistein (a broad-range inhibitor of tyrosine kinases) and **tyrphostin AG-1478** (a specific inhibitor of EGF-receptor tyrosine kinase). Genistein significantly decreased SP-A and SP-A mRNA levels without affecting either tissue viability or the morphol. differentiation of alveolar type II cells. **Tyrphostin AG-1478** also decreased SP-A content and SP-A mRNA levels in cultured fetal **lung** explants. Treatment with EGF could not overcome the inhibitory effects of either genistein or **tyrphostin** on SP-A; however, only **tyrphostin** inhibited EGF-receptor tyrosine phosphorylation. We conclude that specific inhibition of EGF-receptor tyrosine kinase with **tyrphostin AG-1478** blocks the expression of SP-A during spontaneous differentiation of cultured human fetal **lung** tissue. Furthermore, exposure to genistein also decreases SP-A expression and blocks the effects of EGF in human fetal **lung** tissue without inhibiting EGF-receptor tyrosine phosphorylation. These findings support the importance of tyrosine kinase-dependent signal transduction pathways in the regulation of SP-A during human fetal **lung** development.

L49 ANSWER 16 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:263670 HCAPLUS

DN 129:1006
TI Calcium-dependent epidermal growth factor receptor transactivation mediates the angiotensin II-induced mitogen-activated protein kinase activation in vascular smooth muscle cells
AU Eguchi, Satoru; Numaguchi, Kotaro; Iwasaki, Hiroaki; Matsumoto, Takeshi; Yamakawa, Tadashi; Utsunomiya, Hirotoshi; Motley, Evangeline D.; Kawakatsu, Hisaaki; Owada, Koji M.; Hirata, Yuko; Marumo, Fumiaki; Inagami, Tadashi
CS Dep. Biochemistry, Vanderbilt Univ. School Medicine, Nashville, TN, 37232, USA
SO J. Biol. Chem. (1998), 273(15), 8890-8896
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB We have recently reported that angiotensin II (Ang II)-induced mitogen-activated protein kinase (MAPK) activation of a protein tyrosine kinase through Gq-coupled Ang II type 1 receptor in cultured rat vascular smooth muscle cells (VSMC). In the present study, we found Ang II rapidly induced the tyrosine phosphorylation of the epidermal growth factor (EGF) receptor and its assocn. with Shc and Grb2. These reactions were inhibited by the EGF receptor kinase inhibitor, **AG1478**. The Ang II-induced phosphorylation of the EGF receptor was mimicked by a Ca2+ ionophore and completely inhibited by an intracellular Ca2+ chelator. Thus, **AG1478** abolished the MAPK activation induced by Ang II, a Ca2+ ionophore as well as EGF but not by a phorbol ester or platelet-derived growth factor-BB in the VSMC. Moreover, Ang II induced assocn. of EGF receptor with catalytically active c-Src. This reaction was not affected by **AG1478**. These data indicate that Ang II induces Ca2+-dependent transactivation of the EGF receptor which serves as a scaffold for pre-activated c-Src and for down-stream adaptors, leading to MAPK activation in VSMC.

L49 ANSWER 17 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:244442 HCAPLUS
DN 129:36175
TI Preferential inhibition of glioblastoma cells with wild-type epidermal growth factor receptors by a novel tyrosine kinase inhibitor ethyl-2,5-dihydroxycinnamate
AU Han, Yuchun; Caday, Cornelio G.; Umezawa, Kazuo; Nanda, Anil
CS Department of Neurosurgery, Louisiana State University Medical Center, Shreveport, LA, 71130, USA
SO Oncol. Res. (1997), 9(11/12), 581-587
CODEN: ONREE8; ISSN: 0965-0407
PB Cognizant Communication Corp.
DT Journal
LA English
AB Epidermal growth factor receptor (EGFR) gene overexpression and mutations play an important role in the pathogenesis of a variety of malignant human cancers. In this study, we tested the effects of a novel EGFR tyrosine kinase inhibitor, ethyl-2,5-dihydroxycinnamate (EtDHC), against related human glioblastoma cell lines expressing specific forms of EGFR gene mutations. EtDHC more potently inhibited cell growth and DNA synthesis in glioblastoma cells with endogenous or overexpressed wild-type EGFR compared with those with truncated EGFR, by preferentially inhibiting the tyrosine kinase activity and autophosphorylation of the wild-type EGFR. Higher concns. of EtDHC were required to inhibit cells expressing the truncated EGFR. These findings are the reverse of another highly specific tyrosine kinase inhibitor, **tyrphostin AG 1478**

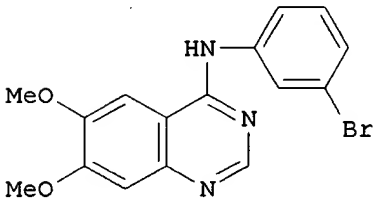
, which preferentially inhibited glioblastoma cells with truncated EGFR compared with those with wild-type EGFR. The differential susceptibility of various glioblastoma cells to highly specific tyrosine kinase inhibitors is significant because human **gliomas** are composed of heterogeneous cells with subsets of cells expressing specific gene mutations. This cellular heterogeneity could be one of the reasons why tumor cells are resistant to chemotherapy. Thus, EtDHC, esp. when in combination with drugs targeting other specific gene mutations (such as **tyrphostin AG 1478**), holds a significant potential for chemotherapy for human glioblastomas.

L49 ANSWER 18 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:240277 HCAPLUS
DN 129:972
TI Angiotensin II type 1 receptor mediates cell proliferation via protein tyrosine kinase and voltage-dependent calcium channels
AU Ozawa, Yashuhir; Suzuki, Yasuyuki; Murakami, Kazuo; Miyazaki, Hitohsi
CS Institute Applied Biochemistry, Gene Experiment Center, University Tsukuba, Ibaraki, 305-0006, Japan
SO Biomed. Res. (1998), 19(1), 1-8
CODEN: BRESD5; ISSN: 0388-6107
PB Biomedical Research Foundation
DT Journal
LA English
AB The authors examd. the signaling pathway mediated by angiotensin II (Ang II) type 1 receptor (AT1) leading to Ang II-induced proliferation of PC12 cells stably expressing the recombinant AT1 receptor (PC12/rAT1). The cell no. increased to 2.4-fold over the control 4 days after Ang II addn. Ang II-induced [3H]thymidine incorporation was affected neither by pertussis toxin nor by calphostin C, a protein kinase C (PKC) inhibitor. In contrast, the Ang II effect was almost completely inhibited by the protein tyrosine kinase (PTK) inhibitor genistein. In addn., tyrphostin **AG1478**, an epidermal growth factor (EGF) receptor-selective inhibitor, significantly inhibited Ang II-induced [3H]thymidine incorporation but had no effect on the basic fibroblast growth factor action. Nicardipine, an L-type Ca2+ channel blocker, also inhibited the Ang II function. Together, these data demonstrate that Gi proteins and PKC are not involved in Ang II-induced cell proliferation of PC12/rAT1 cells through the AT1 receptor, and that Ca2+ influx through voltage-dependent Ca2+ channels and activation of PTK(s) are crit. for this process. Furthermore, the authors' data suggest that ligand-independent activation of a receptor tyrosine kinase(s), called transactivation, plays an important role in AT1-mediated cell proliferation through Gq proteins.

L49 ANSWER 19 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:180763 HCAPLUS
DN 128:261949
TI Use of quinazoline derivatives for the manufacture of a medicament in the treatment of hyperproliferative skin disorders
IN McMahon, Gerald; Shawver, Laura Kay; Narog, Blair; Tang, Peng Cho; Hirth, Klaus Peter
PA Sugen, Inc., USA
SO PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	WO 9810767	A2	19980319	WO 97-US16145	19970911
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9743429	A1	19980402	AU 97-43429	19970911
PRAI	US 96-26067	19960913			
	US 96-31436	19961120			
	US 97-34981	19970108			
	US 97-48372	19970603			
	WO 97-US16145	19970911			
OS	MARPAT 128:261949				
GI					



I

AB Quinazolines, e.g. I, useful for treating hyperproliferative skin disorders, are prepd. Thus, Me 2-amino-4,5-dimethoxybenzoate was cyclocondensed with formamidine acetate to give 6,7-dimethoxy-4-quinazolone, which was chlorinated with thionyl chloride to give the 4-chloro compd. The latter compd. was aminated with 3-bromoaniline to give I-HCl, which was converted to the free base. The quinazolines inhibit epidermal growth factor (EGF) receptor phosphorylation as well as EGF-mediated skin cell growth and psoriatic skin cell proliferation. Specifically, I potently inhibited ligand-induced autophosphorylation of the EGF receptor, and downstream signal transduction events, including DNA replication and cell cycle progression. I was specific for the EGF receptor. Radiolabeled I penetrated human cadaver skin, reaching biol. effective concs. in the epidermis within a 24-h period. A topical formulation contains I 1.0, mineral oil 5.00, glyceryl monostearate 3.00, benzyl alc. 0.75, oleic acid 2.50, butylated hydroxytoluene 0.001 and white petrolatum qs to 100%.

IT **153436-53-4P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of quinazolines for the treatment of hyperproliferative skin disorders)

L49 ANSWER 20 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:130902 HCAPLUS
DN 128:239877
TI The G-protein G13 but not G12 mediates signaling from lysophosphatidic acid receptor via epidermal growth factor receptor to Rho
AU Gohla, Antje; Harhammer, Rainer; Schultz, Gunter
CS Institut fur Pharmakologie, Freie Universitat Berlin, Berlin, D-14195,

Germany
SO J. Biol. Chem. (1998), 273(8), 4653-4659
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Lysophosphatidic acid (LPA) utilizes a G-protein-coupled receptor to activate the small GTP-binding protein Rho and to induce rapid remodeling of the actin cytoskeleton. The authors studied the signal transduction from LPA receptors to Rho activation. Anal. of the G-protein-coupling pattern of LPA receptors by labeling activated G-proteins with [.alpha.-32P]GTP azidoanilide revealed interaction with proteins of the Gq, Gi, and G12 subfamilies. The authors could show that in COS-7 cells, expression of GTPase-deficient mutants of G.alpha.12 and G.alpha.13 triggered Rho activation as measured by increased Rho-GTP levels. In Swiss 3T3 cells, incubation with LPA or microinjection of constitutively active mutants of G.alpha.12 and G.alpha.13 induced formation of actin stress fibers and assembly of focal adhesions in a Rho-dependent manner. Interestingly, the LPA-dependent cytoskeletal reorganization was suppressed by microinjected antibodies directed against G.alpha.13, whereas G.alpha.12-specific antibodies showed no inhibition. The tyrosine kinase inhibitor **tyrphostin** A 25 and the epidermal growth factor (EGF) receptor-specific **tyrphostin AG 1478** completely blocked actin stress fiber formation caused by LPA or activated G.alpha.13 but not the effects of activated G.alpha.12. Also, expression of the dominant neg. EGF receptor mutant EGFR-CD533 markedly prevented the LPA- and G.alpha.13-induced actin polymn. Coexpression of EGFR-CD533 and activated G.alpha.13 in COS-7 cells resulted in decreased Rho-GTP levels compared with expression of activated G.alpha.13 alone. These data indicate that in Swiss 3T3 cells, G13 but not G12 is involved in the LPA-induced activation of Rho. Moreover, the authors' results suggest an involvement of the EGF receptor in this pathway.

L49 ANSWER 21 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:108477 HCAPLUS
DN 128:226630
TI Decorin activates the epidermal growth factor receptor and elevates cytosolic Ca2+ in A431 carcinoma cells
AU Patel, Sandip; Santra, Manoranjan; McQuillan, David J.; Iozzo, Renato V.; Thomas, Andrew P.
CS Department Pathology, Anatomy, Cell Biology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, 19107, USA
SO J. Biol. Chem. (1998), 273(6), 3121-3124
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Several independent lines of evidence have implicated decorin, a small leucine-rich proteoglycan, in the inhibition of cell proliferation. However, the mechanism by which decorin mediates its effect on cell proliferation is unclear. Here the authors report, for the first time, decorin-mediated increases in intracellular Ca2+ levels of single A431 cells. The effects of decorin persisted in the absence of extracellular Ca2+ but were blocked by **AG1478**, an epidermal growth factor (EGF)-specific tyrosine kinase inhibitor, and by down-regulation of the EGF receptor. The effects of decorin were not mimicked by the structurally homologous protein, biglycan. The authors' results indicate a novel action of decorin on the EGF receptor, which results in mobilization of intracellular Ca2+ providing a possible mechanism by which

decorin causes growth suppression.

L49 ANSWER 22 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1998:105843 HCAPLUS
DN 128:136497
TI Aryl and heteroaryl quinazoline compounds which inhibit EGF and/or PDGF receptor tyrosine kinase
IN Myers, Michael R.; Spada, Alfred P.; Maguire, Martin P.; Persons, Paul E.
PA Rhone-Poulenc Rorer Pharmaceuticals Inc., USA
SO U.S., 19 pp. Cont.-in-part of U.S. 5,480,883.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5710158	A	19980120	US 94-229886	19940419
	US 5480883	A	19960102	US 93-166199	19931210
	WO 9515758	A1	19950615	WO 94-US14180	19941208
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN				
	RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9513050	A1	19950627	AU 95-13050	19941208
	EP 871448	A1	19981021	EP 95-904308	19941208
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
	US 5656643	A	19970812	US 95-385258	19950208
	US 5714493	A	19980203	US 96-652444	19960604
PRAI	US 91-698420	19910510			
	US 92-988515	19921210			
	US 93-166199	19931210			
	US 93-146072	19931108			
	US 94-229886	19940419			
	WO 94-US14180	19941208			

OS MARPAT 128:136497
AB This invention relates to the modulation and/or inhibition of cell signaling, cell proliferation, cell inflammatory response, the control of abnormal cell growth and cell reprodn. More specifically, this invention relates to the use of mono- and/or bicyclic aryl or heteroaryl quinazoline compds. in inhibiting cell proliferation, including compds. which are useful protein tyrosine kinase (PTK) inhibitors. The method of treating cell proliferation using said quinazoline compds. and their use in pharmaceutical compns. is described. A no. of compds. were tested for inhibition of PDGF receptor cell-free antophosphorylation procedure.
IT **153436-53-4**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aryl and heteroaryl quinazoline compds. which inhibit EGF and/or PDGF receptor tyrosine kinase)

L49 ANSWER 23 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:790791 HCAPLUS
DN 128:100303
TI Heat shock activates c-Src tyrosine kinases and phosphatidylinositol 3-kinase in NIH3T3 fibroblasts
AU Lin, Richard Z.; Hu, Zhuo-Wei; Chin, Jane H.; Hoffman, Brain B.
CS Veterans Affairs Palo Alto Health Care System and Geriatrics Research,

Education and Clinical Center, Palo Alto, CA, 94304, USA
SO J. Biol. Chem. (1997), 272(49), 31196-31202
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB There is increasing evidence that cellular responses to stress are in part regulated by protein kinases, although specific mechanisms are not well defined. The purpose of these expts. was to investigate potential upstream signaling events activated during heat shock in NIH3T3 fibroblasts. Expts. were designed to ask whether heat shock activates p60 c-Src tyrosine kinase or phosphatidylinositol 3-kinase (PI 3-kinase). Using in vitro protein kinase activity assays, it was demonstrated that heat shock stimulates c-Src and PI 3-kinase activity in a time-dependent manner. Also, there was increased PI 3-kinase activity in anti-phosphotyrosine and anti-c-Src immunopptd. immunocomplexes from heated cells. Heat shock activated mitogen-activated protein kinase (MAPK) and p70 S6 kinase (S6K) in these cells. The role of PI 3-kinase in regulating heat shock activation of MAPK and p70 S6K was investigated using wortmannin, a specific pharmacol. inhibitor of PI 3-kinase. The results demonstrated that wortmannin inhibited heat shock activation of p70 S6K but only partially inhibited heat activation of MAPK. A dominant neg. Raf mutant inhibited activation of MAPK by heat shock but did not inhibit heat shock stimulation of p70 S6K. Genistein, a tyrosine kinase inhibitor, and suramin, a growth factor receptor inhibitor, both inhibited heat shock stimulation of MAPK activity and tyrosine phosphorylation of MAPK. Furthermore, a selective epidermal growth factor receptor (EGFR) inhibitor, tryphostin **AG1478**, and a dominant neg. EGFR mutant also inhibited heat shock activation of MAPK. Heat shock induced EGFR phosphorylation. These results suggest that early upstream signaling events in response to heat stress may involve activation of PI 3-kinase and tyrosine kinases, such as c-Src, and a growth factor receptor, such as EGFR; activation of important downstream pathways, such as MAPK and p70 S6K, occur by divergent signaling mechanisms similar to growth factor stimulation.

L49 ANSWER 24 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:777972 HCAPLUS
DN 128:87028
TI Role of heparin-binding EGF-related peptides in proliferation and **apoptosis** of activated ras-stimulated intestinal epithelial cells
AU Zushi, Shinichiro; Shinomura, Yasuhisa; Kiyohara, Tatsuya; Miyazaki, Yoshiji; Tsutsui, Shusaku; Sugimachi, Masamitsu; Higashimoto, Yoshifumi; Kanayama, Shuji; Matsuzawa, Yuji
CS Second Department of Internal Medicine, Osaka University Medical School, Suita, 565, Japan
SO Int. J. Cancer (1997), 73(6), 917-923
CODEN: IJCNAW; ISSN: 0020-7136
PB Wiley-Liss, Inc.
DT Journal
LA English
AB The ras mutation is a common and crit. step in carcinogenesis. Autocrine growth factors are also known to play an important role in cancer cell growth and transformation. However, the contribution of autocrine growth factors in regulation of proliferation and **apoptosis** of activated ras-stimulated intestinal epithelium is not fully understood. Therefore, we constructed activated ras-transfected intestinal epithelial cell clones (IEC-ras) to examine the role of epidermal growth factor (EGF)-related peptides in the behavior of IEC-ras. Overexpression of EGF

family growth factors (transforming growth factor .alpha., heparin-binding EGF-like growth factor, amphiregulin, and betacellulin) and stronger phosphorylation of the EGF receptor was obsd. in IEC-ras compared with control cells. IEC-ras proliferated more rapidly than control cells, and a specific EGF receptor kinase inhibitor, **AG 1478**, abolished the increased proliferation of IEC-ras. Heparitinase and chlorate also prevented increased proliferation of IEC-ras. Addnl., IEC-ras expressed more bcl-2 and was more resistant to **apoptosis** induction by UV radiation and mitomycin C. **AG 1478** suppressed bcl-2 expression and inhibited resistance to **apoptosis** of IEC-ras. Heparitinase and chlorate had effects similar to those of **AG 1478**. Our data indicate that heparin-binding EGF family growth factors play an important role in both increased proliferation and resistance to **apoptosis** of ras-stimulated intestinal epithelial cells.

L49 ANSWER 25 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:685839 HCAPLUS
DN 127:355628
TI Rapid stimulation of amyloid precursor protein release by epidermal growth factor: role of protein kinase C
AU Slack, Barbara E.; Breu, Jeffrey; Muchnicki, Lisa; Wurtman, Richard J.
CS Department Pathology Laboratory Medicine, Boston University School Medicine, Boston, MA, 02118, USA
SO Biochem. J. (1997), 327(1), 245-249
CODEN: BIJOAK; ISSN: 0264-6021
PB Portland Press
DT Journal
LA English
AB The amyloid precursor protein (APP) of Alzheimer's disease is a transmembrane protein that is cleaved by an uncharacterized enzyme known as .alpha.-secretase within its extracellular/intraluminal domain after the activation of guanine nucleotide-binding protein-coupled receptors linked to phosphoinositide hydrolysis. The secretory process results in the release of large sol. derivs. of APP (APPs), and, when elicited by muscarinic receptor activation, exhibits both protein kinase C (PKC)-dependent and tyrosine phosphorylation-dependent components. In this report the authors examine the regulation of the release of APPs by epidermal growth factor (EGF) receptors, which possess intrinsic tyrosine kinase activity, and are coupled to a variety of effectors including phosphoinositide-specific phospholipase C.gamma.. In A431 cells, EGF caused time-dependent and dose-dependent increases in the formation of inositol phosphates in cultures prelabeled with myo-[3H]inositol, and in the release of APPs into the culture medium; the two responses exhibited similar time courses and EC50 values for EGF. Concomitant with these effects, there were concn.-dependent (3-300 ng/mL) increases in the phosphorylation of tyrosine residues in several proteins, including the EGF receptor itself. The specific PKC antagonist GF 109203X decreased the effect of EGF by approx. 35% at a concn. that abolished the stimulation of the release of APPs by the PKC activator PMA. **Tyrphostin AG 1478**, an inhibitor of EGF receptor tyrosine kinase, abolished the EGF-induced release of APPs. These results demonstrate that in A431 cells, activation of the EGF receptor stimulates .alpha.-secretase activity by a mechanism that is partly dependent on PKC activity.

L49 ANSWER 26 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:633638 HCAPLUS
DN 127:303635
TI EGF receptor ligands are a large fraction of in vitro branching morphogens

secreted by embryonic kidney
AU Sakurai, Hiroyuki; Tsukamoto, Tatsuo; Kjelsberg, Crystal A.; Cantley, Lloyd G.; Nigam, Sanjay K.
CS Renal Division, Dep. Medicine, Brigham and Women's Hospital, Boston, MA, 02115, USA
SO Am. J. Physiol. (1997), 273(3, Pt. 2), F463-F472
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
AB Much attention has recently focused upon hepatocyte growth factor (HGF) as a potential regulator of epithelial branching morphogenesis. However, since neither the HGF nor c-met "knockout" mice show abnormal kidney branching morphogenesis, the authors sought to analyze the relative importance of HGF in in vitro branching morphogenesis compared with other factors secreted by the embryonic kidney. Exploiting an assay that employs kidney epithelial cells (murine inner medullary collecting duct, mIMCD3) seeded in collagen cocultured with the embryonic kidney, the authors found that a tyrosine kinase inhibitor that is highly specific for the epidermal growth factor (EGF) receptor (EGFR), tyrphostin **AG1478**, inhibited mIMCD3 cell process formation (an early step in branching tubulogenesis) by 40%, whereas high concns. of neutralizing anti-HGF antibodies had a lesser effect (20% inhibition), suggesting that EGFR ligands account for a larger fraction of branching morphogens secreted by the embryonic kidney than HGF. In addn., when an embryonic epithelial cell line derived from c-met (-/-) mice was cocultured with the embryonic kidney, these c-met (-/-) cells underwent process formation. EGFR ligands but not HGF were able to induce branching tubulogenesis in these cells. All EGFR ligands tested, including EGF, transforming growth factor-.alpha., heparin-binding EGF, betacellulin, and amphiregulin, induced mIMCD3 cell tubulogenesis. EGFR ligands caused upregulation of urokinase, urokinase receptor, and matrix metalloprotease-1, and tubulogenesis could be inhibited by the metalloprotease inhibitor, 1,10-phenanthroline. The authors' results support the notion that multiple parallel and potentially redundant growth factor-dependent pathways regulate branching tubulogenesis.

L49 ANSWER 27 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:625097 HCAPLUS
DN 127:259484
TI Radiation-induced proliferation of the human A431 squamous carcinoma cells is dependent on EGFR tyrosine phosphorylation
AU Schmidt-Ullrich, R. K.; Mikkelsen, R. B.; Dent, P.; Todd, D. G.; Valerie, K.; Kavanagh, B. D.; Contessa, J. N.; Rorrer, W. K.; Chen, P. B.
CS Department of Radiation Oncology, Medical College of Virginia/Virginia Commonwealth University, Richmond, VA, 23298-0058, USA
SO Oncogene (1997), 15(10), 1191-1197
CODEN: ONCNES; ISSN: 0950-9232
PB Stockton
DT Journal
LA English
AB Accelerated cellular repopulation has been described as a response of tumors to fractionated irradn. in both normal tissue and tumor systems. To identify the mechanisms by which cells enhance their proliferative rate in response to clin. used doses of ionizing radiation (IR) (.gamma.-rays) we have studied human **mammary** and squamous carcinoma cells which are autocrine growth regulated by the epidermal growth factor receptor (EGFR) and its ligands, transforming growth factor-.alpha. and EGF. Both EGF and IR induced EGFR autophosphorylation, comparable levels of

phospholipase C.gamma. activation as measured by inositol-1,4,5-triphosphate prodn., and as a consequence oscillations in cytosolic [Ca2+]. Activities of Raf-1 and mitogen-activated protein kinase (MAPK) were also stimulated by EGF and IR by Ca2+-dependent mechanisms. All these responses to EGF and IR were dependent upon activation of EGFR as judged by the use of the specific inhibitor of EGFR autophosphorylation, tyrphostin **AG1478**. Importantly, IR-induced proliferation of A431 cells was also inhibited by **AG1478**. This is the first report which demonstrates a link between IR-induced activation of proliferative signal transduction pathways and enhanced proliferation. We propose that accelerated repopulation of tumors whose growth is regulated by EGFR is initiated by an IR-induced EGFR activation mechanism that mimics the effects of growth factors.

L49 ANSWER 28 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:621104 HCAPLUS
DN 127:303614
TI Unliganded epidermal growth factor receptor dimerization induced by direct interaction of quinazolines with the ATP binding site
AU Arteaga, Carlos L.; Ramsey, Timothy T.; Shawver, Laura K.; Guyer, Cheryl A.
CS Departments of Medicine and Cell Biology, Vanderbilt Cancer Center and the Department of Veteran Affairs Medical Center, Vanderbilt University School of Medicine, Nashville, TN, 37232-5536, USA
SO J. Biol. Chem. (1997), 272(37), 23247-23254
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Receptor dimerization is crit. for signaling by the epidermal growth factor receptor (EGFR) tyrosine kinase. This occurs after binding of the receptor's extracellular domain by ligand or bivalent antibodies. The role of other receptor domains in dimerization is less clear, and there are no examples of dimers induced by direct perturbation of the EGFR kinase domain. Submicromolar concns. of **AG-1478** and AG-1517, quinazolines specific for inhibition of the EGFR kinase, induced reversible receptor dimerization in vitro and in intact A431 cells. Consistent with the inhibitory effect of quinazolines on receptor kinase activity, the dimers formed lacked a detectable Tyr(P) signal. Quinazoline-induced EGFR dimerization was abrogated in vitro by ATP and the ATP analog adenyl-5'-yl imidodiphosphate. Receptors with a single-point mutation in the ATP binding site as well as wild-type EGFR with a covalent modification of the ATP site failed to dimerize in response to **AG-1478** and AG-1517. These data suggest that EGFR dimerization can be induced by the interaction of quinazolines at the ATP site in the absence of receptor ligand binding. In SKBR-3 cells, the quinazolines induced the formation of inactive EGFR/ErbB-2 heterodimers, potentially sequestering ErbB-2 from interacting with other coreceptors of the ErbB family. Structural studies of the quinazoline interaction with the EGFR tyrosine kinase domain should allow for an anal. of receptor-specific chem. features required for binding to the ATP site and disruption of signaling, a strategy that can be perhaps applied to other tumor cell receptor systems.
IT **153436-53-4, AG 1478**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(EGF receptor dimerization induction by quinazoline interaction with ATP binding site)

L49 ANSWER 29 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:560273 HCAPLUS
DN 127:246318
TI Two- and three-dimensional cell structures govern epidermal growth factor survival function in human bladder carcinoma cell lines
AU Dangles, Virginie; Femenia, Francoise; Laine, Veronique; Berthelemy, Madeleine; Le Rhun, Danielle; Poupon, Marie-France; Levy, Daniel; Schwartz-Cornil, Isabelle
CS URA INRA-DGER d'Immunopathologie Cellulaire et Moleculaire, Ecole Nationale Veterinaire, Maisons Alfort, 94704, Fr.
SO Cancer Res. (1997), 57(16), 3360-3364
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB Human bladder carcinomas often express high levels of the epidermal growth factor (EGF) receptor. In three human bladder carcinoma cell lines (OBR, T24, and 647V), the authors show that two EGF receptor ligands, namely EGF and transforming growth factor .alpha., enhanced the **apoptosis** due to serum starvation on cells cultured as monolayers. Conversely, EGF and transforming growth factor .alpha. prevented **apoptosis** when the same serum-starved cells were cultured as three-dimensional spheroids. Both stimulation and inhibition of **apoptosis** by EGF were assocd. with p21 WAF1/CIP1 overexpression. In 647V spheroids, EGF protection against radiation-induced **apoptosis** was negated by genistein and tyrphostin **AG1478**, suggesting that blockade of the EGF signal transduction in patients with bladder cancer may improve the radiotherapy efficacy.

L49 ANSWER 30 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:394672 HCAPLUS
DN 127:90966
TI An in vitro tubulogenesis system using cell lines derived from the embryonic kidney shows dependence on multiple soluble growth factors
AU Sakurai, Hiroyuki; Barros, Elvino J.; Tsukamoto, Tatsuo; Barasch, Jonathan; Nigam, Sanjay K.
CS Renal Division, Department Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, 02115, USA
SO Proc. Natl. Acad. Sci. U. S. A. (1997), 94(12), 6279-6284
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB Interactions between the ureteric bud (UB) and metanephric mesenchyme are crucial for tubulogenesis during kidney development. Two immortalized cell lines derived from the day 11.5 embryonic kidney, UB cells, which appear to be epithelial (cytokeratin-pos., E-cadherin-pos., and ZO-1-pos. by immunostaining) and BSN cells, which are largely mesenchymal (vimentin-pos., but neg. for cytokeratin, cell surface E-cadherin, and cell surface ZO-1), were used to establish an in vitro tubulogenesis system. BSN cells expressed hepatocyte growth factor (HGF) and transforming growth factor-.beta.1 mRNAs, and its conditioned medium (BSN-CM) contained factors capable of activating the epidermal growth factor (EGF) receptor (EGFR). When UB cells were cultured in an extracellular matrix gel in the presence of the embryonic kidney or BSN-CM, the UB cells underwent morphogenetic changes characteristic of early in vitro branching tubulogenesis. These changes were largely inhibited by a combination of neutralizing anti-HGF antibodies and the EGFR inhibitor tyrphostin **AG1478**, suggesting that EGFR ligands,

together with HGF, account for much of this early morphogenetic activity. Nevertheless, there was a significant fraction of tubulogenic activity that could not be inhibited, suggesting the existence of other sol. factors. Whereas HGF, EGF, transforming growth factor .alpha., basic fibroblast growth factor (bFGF), and insulin-like growth factor 1 (IGF-1), or a mixt. of these growth factors, induced epithelial processes for up to 3 days, only IGF-1, possibly bFGF, and the mixt. were able to sustain morphogenesis for longer periods, though not nearly to the same degree as BSN-CM. Moreover, only BSN-CM induced branching tubular structures with clear lumens, consistent with the existence of other sol. factors crucial for the formation and/or maintenance of branching tubular structures with lumens in vitro.

L49 ANSWER 31 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:296186 HCAPLUS
DN 127:757
TI Opposing effects of tyrosine kinase inhibitors on mineralization of normal and tumor bone cells
AU Klein, B. Y.; Tepper, S.H.; Gal, I.; Shlomai, Z.; Ben-Bassat, H.
CS Laboratory of Experimental Surgery, Hadassah Medical Center, Jerusalem, 12000, Israel
SO J. Cell. Biochem. (1997), 65(3), 420-429
CODEN: JCEBD5; ISSN: 0730-2312
PB Wiley-Liss
DT Journal
LA English
AB Induction of matrix maturation and mineralization in calcified tissues is important for patients with primary bone tumors and other bone deficiencies, e.g., osteoporosis. For the former it signifies a better prognosis in osteosarcoma, and for the latter it might improve bone remodeling. In the present study we exposed osteosarcoma cells (Saos2), normal bone cells, and marrow stroma to two different tyrosine kinase (TK) inhibitors: AG-555 and **AG-1478**. These **tyrphostins** differ in their effect on signal transduction downstream to the TK receptor (RTK): **AG-1478** inhibits src family TKs whereas AG-555 inhibits nuclear TKs. We found that both **tyrphostins** at 50 .mu.M increased specific alk. phosphatase (ALP) activity in Saos2 cells. AG-555 abrogated mineralization whereas **AG-1478** increased it. Similarly, in human bone-derived cell cultures the same dose of **tyrphostins** had an opposing effect on mineralization but, in contrast to AG-555, **AG-1478** pos. selected cells with ALP activity. These **tyrphostins** also differed in their effect on rat marrow stromal cells. AG-555 decreased cell counts unselectively, whereas the decreased cell counts by **AG-1478** resulted in selection of osteoprogenitor cells as indicated by a concordant increase in specific ALP activity. The effect of a lower dose of **AG-1478**, 5 .mu.M, on the increase in mineralization exceeded its own efficiency in selecting cells with specific ALP activity. Our results indicate that **AG-1478** selects and preserves the osteoblastic phenotype, at doses moderately higher than those required to induce mineralization, and substantially higher than the doses required for RTK inhibition. Identification of downstream mol. targets for **AG-1478**, in marrow stromal cells, might prove useful in designing more selective drugs, capable of sepg. proliferative from differentiation-inducing activities.
IT **153436-53-4, AG 1478**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(tyrosine kinase inhibitors opposing effects on mineralization of normal and tumor bone cells)

L49 ANSWER 32 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:123274 HCAPLUS
DN 126:207777
TI EGF-R dependent regulation of keratinocyte survival
AU Rodeck, Ulrich; Jost, Monika; Kari, Csaba; Shih, Daw-Tsun; Lavker, Robert M.; Ewert, Donald L.; Jensen, Pamela J.
CS The Wistar Institute, Philadelphia, PA, 19104, USA
SO J. Cell Sci. (1997), 110(2), 113-121
CODEN: JNCSAI; ISSN: 0021-9533
PB Company of Biologists
DT Journal
LA English
AB Tissue organization and maintenance within multicellular organisms is in part dependent on the ability of **cells** to undergo programmed **cell death** or **apoptosis**. Conversely, disruption of **cell death** pathways often is assocd. with tumor development. At present, the mol. control of **apoptosis** in epithelial **cells** is poorly understood. Here the authors describe evidence linking epidermal growth factor-receptor (EGF-R) activation to survival of normal human keratinocytes in culture. Inhibition of EGF-R activation by an anti-EGF-R antagonistic monoclonal antibody (mAb 425), followed by detachment of keratinocytes from the substratum, induced extensive **death** with several features of **apoptosis** in keratinocyte cultures. Other, non-epithelial normal human **cells** including melanocytes and fibroblasts, did not show this effect. Similar to EGF-R blockade by mAb 425, inhibition of the EGF-R tyrosine kinase activity using tyrphostin **AG1478** resulted in lack of attachment and extensive **cell death** upon passaging. Attachment to keratinocyte-derived ECM partially rescued mAb 425-treated keratinocytes from **cell death**, indicating that adhesion-dependent and EGF-R-dependent signal transduction pathways serve partially overlapping but not redundant roles in supporting keratinocyte survival.

L49 ANSWER 33 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1997:92866 HCAPLUS
DN 126:181747
TI Inhibition of tyrosine kinase activity decreases expression of surfactant protein A in a human **lung** adenocarcinoma cell line independent of epidermal growth factor receptor
AU Klein, Jonathan M.; McCarthy, Troy A.
CS Department of Pediatrics, University of Iowa, 200 Hawkins Drive, Iowa City, Iowa 52242-1083, USA
SO Biochim. Biophys. Acta (1997), 1355(3), 218-230
CODEN: BBACAQ; ISSN: 0006-3002
PB Elsevier
DT Journal
LA English
AB Epidermal growth factor (EGF) enhances fetal **lung** development in vivo and in vitro. Ligand binding to the EGF receptor stimulates an intrinsic receptor tyrosine kinase initiating a signal transduction cascade. We hypothesized that blocking EGF receptor function with tyrosine kinase inhibitors would decrease the expression of surfactant protein A in human pulmonary epithelial cells. Human pulmonary adenocarcinoma cells (NCI-H441) were exposed to genistein (a broad range inhibitor of tyrosine kinases) and tyrphostin **AG1478** (a specific

inhibitor of EGF receptor tyrosine kinase). Genistein significantly decreased surfactant protein A (SP-A) and SP-A mRNA levels in H441 cells without affecting cell viability. The inhibitory effect of genistein on SP-A content was reversible. In contrast, tyrphostin **AG1478** had no effect on SP-A levels despite a greater inhibitory effect than genistein on EGF receptor tyrosine autophosphorylation. Furthermore, treatment of H441 cells with exogenous EGF did not increase SP-A content or mRNA levels beyond baseline. We conclude that inhibition of tyrosine kinase activity other than the EGF receptor decreases the expression of surfactant protein A at a pretranslational level in human pulmonary adenocarcinoma cells. These results suggest the importance of tyrosine kinases in modulating human SP-A synthesis.

L49 ANSWER 34 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:739544 HCAPLUS
DN 126:43844
TI Asbestos causes stimulation of the extracellular signal-regulated kinase 1 mitogen-activated protein kinase cascade after phosphorylation of the epidermal growth factor receptor
AU Zanella, Christine L.; Posada, James; Tritton, Thomas, R.; Mossman, Brooke T.
CS Department of Pathology, University of Vermont College of Medicine, Burlington, VT, 05045, USA
SO Cancer Res. (1996), 56(23), 5334-5338
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB The authors examd. signal transduction events induced by asbestos in target cells of mesothelioma and potential cell surface origins for these cascades. Asbestos fibers, but not their nonfibrous analogs, induced protracted phosphorylation of the mitogen-activated protein (MAP) kinases and extracellular signal-regulated kinases (ERK) 1 and 2, and increased kinase activity of ERK2, ERK1 and ERK2 phosphorylation and activity was initiated by addn. of exogenous epidermal growth factor (EGF) and transforming growth factor-.alpha., but not by isoforms of platelet-derived growth factor-1 in mesothelial cells. MAP kinase activation by asbestos was attenuated by suramin, which inhibits growth factor receptor interactions, or **tyrphostin AG 1478**, a specific inhibitor of EGF receptor tyrosine kinase activity (IC530 = 3 nM). Asbestos caused autophosphorylation of the EGF receptor, an event triggering the ERK cascade. These studies are the first to establish that a MAP kinase signal transduction pathway is initiated after phosphorylation of a peptide growth factor receptor following exposure to asbestos fibers.

L49 ANSWER 35 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:116898 HCAPLUS
DN 124:249905
TI Inhibition of acute lymphoblastic leukemia by a Jak-2 inhibitor
AU Meydan, Naftaly; Grunberger, Tom; Dadi, Harjit; Shahar, Michal; Arpaia, Enrico; Lapidot, Zvi; Leeder, J. Steven; Freedman, Melvin; Cohen, Amos; et al.
CS The Hospital for Sick Children, Univ. Toronto, Toronto, M5G 1X8, Can.
SO Nature (London) (1996), 379(6566), 645-8
CODEN: NATUAS; ISSN: 0028-0836
DT Journal
LA English
AB Acute lymphoblastic leukemia (ALL) is the most common cancer of childhood.

Despite the progress achieved in its treatment, 20% of cases relapse and no longer respond to chemotherapy. The most common phenotype of all **cells** share surface antigens with very early precursors of B **cells** and are therefore believed to originate from this lineage. Characterization of the growth requirement of ALL **cells** indicated that they were dependent on various cytokines, suggesting paracrine and/or autocrine growth regulation. Because many cytokines induce tyrosine phosphorylation in lymphoid progenitor **cells**, and constitutive tyrosine phosphorylation is commonly obsd. in B-lineage leukemias, attempts have been made to develop protein tyrosine kinase (PTK) blockers of leukemia **cell** growth. Here the authors show that leukemic **cells** from patients in relapse have constitutively activated Jak-2 PTK. Inhibition of Jak-2 activity by a specific tyrosine kinase blocker, AG-490, selectively blocks leukemic **cell** growth in vitro and in vivo by inducing programmed **cell death** , with no deleterious effect on normal hematopoiesis. None of the other tyrphostins tested had any activity against leukemic **cells**.

IT **175178-82-2, AG 1478**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of acute lymphoblastic leukemia by a Jak-2 protein tyrosine kinase inhibitor AG-490 in relation to screening of other **tyrphostins**)

L49 ANSWER 36 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1996:101240 HCAPLUS
DN 124:136522
TI Role of transactivation of the EGF receptor in signaling by G-protein-coupled receptors
AU Daub, Henrik; Weiss, F. Ulrich; Wallasch, Christian; Ullrich, Axel
CS Dep. Molecular Biol., Max-Planck-Inst. Biochemie, Martinsried, 82152, Germany
SO Nature (London) (1996), 379(6565), 557-60
CODEN: NATUAS; ISSN: 0028-0836
DT Journal
LA English
AB Transduction of a mitogenic signal from the cell membrane to the nucleus involves the adapter proteins SHC and Grb2, which mediate activation of the Ras/mitogen-activated protein (MAP) kinase pathway1-5. In contrast to receptor tyrosine kinases (RTKs), the signaling steps leading to Ras/MAP kinase activation by G-protein-coupled receptors (GPCRs) are still poorly characterized but appear to include .beta..gamma. subunits of heterotrimeric G-proteins and as-yet unidentified tyrosine kinases. The authors report here that the epidermal growth factor receptor (EGFR) and the neu oncoprotein become rapidly tyrosine-phosphorylated upon stimulation of Rat-1 cells with the GPCR agonists endothelin-1, lysophosphatidic acid and thrombin, suggesting that there is an intracellular mechanism for transactivation. Specific inhibition of EGFR function by either the selective tyrphostin **AG1478** or a dominant-neg. EGFR mutant suppressed MAP kinase activation and strongly inhibited induction of fos gene expression and DNA synthesis. The results demonstrate a role for RTKs as downstream mediators in GPCR mitogenic signaling and suggest a ligand-independent mechanism of RTK activation through intracellular signal crosstalk.

L49 ANSWER 37 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1995:827799 HCAPLUS
DN 123:219237
TI Prolonged induction of p21Cip1/WAF1/CDK2/PCNA complex by epidermal growth

factor receptor activation mediates ligand-induced A431 cell growth inhibition
AU Fan, Zhen; Lu, Yang; Wu, Xipu; DeBlasio, Anthony; Koff, Andrew; Mendelsohn, John
CS Program Mol. Pharmacology and Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA
SO J. Cell Biol. (1995), 131(1), 235-42
CODEN: JCLBA3; ISSN: 0021-9525
DT Journal
LA English
AB Proliferation of some cultured human tumor cell lines bearing high nos. of epidermal growth factor (EGF) receptors is paradoxically inhibited by EGF in nanomolar concns. In the present study, the authors have investigated the biochem. mechanism of growth inhibition in A431 human squamous carcinoma cells exposed to exogenous EGF. In parallel, the authors studied a selected subpopulation, A431-F, which is resistant to EGF-mediated growth inhibition. The authors obsd. a marked redn. in cyclin-dependent kinase-2 (CDK2) activity when A431 and A431-F cells were cultured with 20 nM EGF for 4 h. After further continuous exposure of A431 cells to EGF, the CDK2 activity remained at a low level and was accompanied by persistent G1 arrest. In contrast, the early reduced CDK2 activity and G1 accumulation in A431-F cells was only transient. The authors found that, at early time points (4-8 h), EGF induces p21Cip1/WAF1 mRNA and protein expression in both EGF-sensitive A431 cells and EGF-resistant A431-F cells. But only in A431 cells, was p21Cip1/WAF1 expression sustained at a significantly increased level for up to 5 d after addn. of EGF. Induction of p21Cip1/Waf1 by EGF could be inhibited by a specific EGF receptor tyrosine kinase inhibitor, **tyrphostin AG 1478**, suggesting that p21Cip1/WAF1 induction was a consequence of receptor tyrosine kinase activation by EGF. The authors also demonstrated that the increased p21Cip1/WAF1 was assocd. with both CDK2 and proliferating cell nuclear antigen (PCNA). Taken together, the results demonstrate that p21Cip1/WAF1 is an important mediator of EGF-induced G1 arrest and growth inhibition in A431 cells.

L49 ANSWER 38 OF 38 HCAPLUS COPYRIGHT 1999 ACS
AN 1994:217715 HCAPLUS
DN 120:217715
TI Quinazoline tyrosine kinase-inhibiting anticancer agents
IN Barker, Andrew J.
PA Zeneca Ltd., UK
SO Can. Pat. Appl., 99 pp.
CODEN: CPXXEB
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CA 2086968	AA	19930721	CA 93-2086968	19930108
	CA 2086968	C	19980623		
	ZA 9300015	A	19930720	ZA 93-15	19930104
	AU 9331010	A1	19930722	AU 93-31010	19930104
	AU 661533	B2	19950727		
	HU 63153	A2	19930728	HU 93-94	19930115
	EP 566226	A1	19931020	EP 93-300270	19930115
	EP 566226	B1	19951108		
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	ES 2078798	T3	19951216	ES 93-300270	19930115

	CZ 282038	B6	19970416	CZ 93-43	19930118
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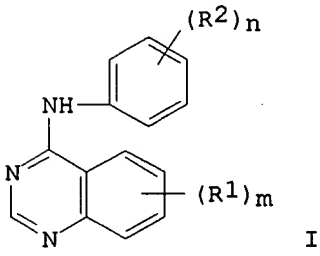
	GB 92-13572	19920626			
	GB 92-23735	19921112			
	US 93-5280	19930119			
	US 94-284293	19940802			
OS	MARPAT 120:217715				
GI					



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AB The title compds. I [R1 = HO, (un)substituted amino, carboxy, carbamoyl, ureido, etc.; R2 = H, HO, halogen, CF3, NH2, NO2, CN, (un)substituted C1-4 alkyl, etc.; m = 1-3; n = 1, 2], useful as tyrosine kinase-inhibiting anticancer agents (no data), are prepd. and I-contg. formulations presented. Thus, 4-chloro-6,7-dimethoxyquinazoline was condensed with 3-MeC6H4NH2, producing 6,7-dimethoxy-4-(3'-methylanilino)quinazoline hydrochloride, m.p. 248-249.degree..

IT **153436-53-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as tyrosine kinase-inhibiting anticancer agent)

IT **153436-53-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(reactant, in prepn. of quinazoline anticancer agents)

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L10	40	SEA FILE=HCAPLUS ABB=ON PLU=ON AG1478 OR AG 1478
L11	12	SEA FILE=HCAPLUS ABB=ON PLU=ON TYRPHOSTIN(L)1478
L12	1	SEA FILE=REGISTRY ABB=ON PLU=ON 153436-53-4/RN
L13	16	SEA FILE=HCAPLUS ABB=ON PLU=ON L12
L19	3	SEA FILE=REGISTRY ABB=ON PLU=ON 15663-27-1 OR 33069-62-4 OR 57-22-7
L50	0	SEA FILE=HCAPLUS ABB=ON PLU=ON (L10 OR L11 OR L13) AND (L19 OR CISPLATIN OR PACLITAXEL OR TAXOL OR VINCRISTIN?)